not only frequent, but also high, doses for therapeutic effect—often so high that initial peak doses cause side effects. Extending half-life of such therapeutics permits lower, less frequent, and therefore potentially safer doses, which are cheaper to produce. "It's clear many if not most human proteins need to be formulated so they last a long time in the human body," says HGS CEO William Haseltine.

Albumin is already incorporated in most protein drug formulations as a stabilizer. Its half-life is about two weeks, and fusing its gene to that of a therapeutic protein exploits its stability in a new way without impeding tertiary folding or compromising therapeutic activity of the resulting protein, according to Haseltine. He says HGS will spend part of the $950 million raised from its stock offering in October on expanding Principia's facilities and personnel to briskly march as many as 20 albumin fusion proteins—based on drugs developed by any company—through phase I trials. Afterwards, says Haseltine, HGS will decide between cutting licensing deals or proceeding alone, patent situations permitting. "We will not try to violate peoples' patents, but we may try to convince them that we have a better drug for them to sell."

Heading the list, already 12 products long, is albuferon, a fusion of interferon alpha and albumin. Inteferon alpha, which generates annual sales of more than $1 billion worldwide for Schering-Plough, has a half-life of less than 2 hours, is cleared by the body in 12, and must therefore be injected several times a week. It is used in a variety of indications, including severe kidney cancer and genital warts—conditions that are aggravated by side effects and frequent administration of the drug. Moreover, difficulty in maintaining a constant level in the blood means that only 10% of patients see sustained viral clearance as a result of treatment for hepatitis C. HGS expects much better performance against the virus from longer-lasting albuferon, which would be administered once every 10 to 15 days, and hopes side effects like myelosuppression and depression will be avoided. Other proteins slated for fusion are Genentech's human growth hormone and Amgen's erythropoietin and granulocyte colony-stimulating factor—drugs with annual sales of about $19 million, $2 billion, and $1 billion, respectively.

Although the recent news has had no apparent impact on HGS stock, Joe Dougherty, analyst at Lehman Brothers (New York), says the clinical data for albuferon is "quite compelling." "These [albumin fusion] drugs are unquestionably patentable on their own and may have improved properties," says Dougherty. Both Amgen and Genentech declined to comment.

However, HGS faces competition from companies offering alternative half-life extension technologies. Neose Technologies (Horsham, PA), for example, has recently begun touting its glycosylation biotechnology, while InfiMed Therapeutics (Cambridge, MA), is developing the use of nanoparticles for sustained protein release.

A more immediate threat could come from companies involved with pegylation, a method of extending half-life by coating proteins with polyethylene glycol. Peg-Intron, Schering-Plough's pegylated interferon alpha, for example, requires a weekly dose and is already under FDA review. Haseltine points out that pegylation is some 20 years old, calling it inferior to albumin fusion in half-life, manufacturing expense, and preservation of therapeutic activity. However, Valentis (Burlingame, CA) has already overcome the problem of denaturation arising from the pegylation process, according to CFO Bennet Weintraub. He says Valentis's process is a world apart from the procedure that plunged the bioactivity yield of Hoffmann-La Roche's pegylated version of interferon alpha to 10%.

In any event, extending half-life is not necessarily advantageous. "If a patient starts to go south because of a drug with a long half-life, you can't quickly get rid of it," says Stewart Lyman, director of extramural research at Immunex (Seattle, WA). "With a short half-life, you at least can put the patient in intensive care knowing tomorrow the drug will be gone." Lyman points to Immunex's Enbrel, a tumor necrosis factor receptor antagonist for treating rheumatoid arthritis. Enbrel's short half-life permits quick curtailment in the instance of a bacterial infection, when it is contraindicated—something that would not be possible if Enbrel had a longer half-life.

As Dougherty summarizes, "It's early days for the [fusion] technology and we don't know how widely applicable it will turn out to be."

Tom Hollon

Chiral drugs viable, despite failure

The business strategies of companies involved in chiral drug development were cast into doubt in October after Eli Lilly (Indianapolis, IL) decided not to pursue the development of R-fluoxetine, Sepracor's (Marlborough, MA) single isomer form of the anti-depressant Prozac. $3.9 billion was wiped off Sepracor's market capitalization as investors called into question the entire utility of single enantiomers as a means of improving drugs and managing product life cycles. However, most analysts say the case is insignificant and cannot be extrapolated to Sepracor's pipeline or those of similar companies.

The business of developing single isomer drugs came about because the chemical production methods used for pharmaceuticals often produced racemic mixtures of two enantiomers. In the case of thalidomide, it was shown that one enantiomer was responsible for efficacy and another for side effects. Companies like Chiroscience (Slough, UK) and Sepracor based businesses on developing single enantiomer versions of old drugs in the hope of improving their pharmakogenetic profile—increasing efficacy and reducing side effects. Because regulatory authorities accept relevant data from clinical trials of racemates, developing chirally pure versions was thought to be a short cut to market—quicker, cheaper, and less risky than other endeavors. Successful examples include Chiroscience's anesthetic levobupivacaine (chirocaine), the single isomer version of Astra's bupivacaine (marcane); it retained all the activity of the racemate but with less cardiotoxicity, thus expanding utility to childbirth, which was contraindicated for Astra's version.

Pharmaceutical companies often try to extend patent life of blockbuster drugs by developing chirally pure versions and moving patients over to them (a process called racemic switching) before the patent on the racemate expires and generics flood the market. AstraZeneca, for instance, has developed esomeprazole (Nexium), a single enantiomer version of its $6 billion anti-ulcer drug omeprazole (Prilosec), which will come off patent in 2002; Nexium was approved in Europe in July and is currently under FDA review.

However, in R-fluoxetine's case, review of clinical data showed a dose-dependent cardiac-related side effect not seen in the racemate; dosing levels had been increased to 8 times the effective dose of Prozac in an effort to get better efficacy, suggesting the single isomer was actually inferior to the racemate. Sepracor share price fell 28% the day of the news, falling a further 22% to $67.31 by November 2. "It was a massive disappointment for shareholders," says Peter Drake, analyst at Prudential Vector Securities (Deerfield, IL). "The overwhelming consensus was that R-fluoxetine was going to be a safe and effective new antidepressant."

But it is not unusual for enantiomers to exhibit more side effects than their racemates. Sandra Erb, manager of Technology Catalysts International (Falls Church, VA), a chiral and fine chemical consulting practise, says BASF, for example, stopped development of Chiroscience's Verapamil, the single enantiomer version of Isoptin after "they were getting some different side effects that were perhaps a little more disturbing." Enantiomers can also be equi-efficacious: Celltech Group

(Slough, UK), for instance, signed a deal on November 10 with Penwest Pharmaceuticals to come up with a way of releasing chiral isomers at differential rates, after discovering that the isomers within its D6428 analgesic are *both* active and have different and complementary profiles. "Just because you have a single isomer doesn't mean you're going to have a drug that is going to be safer and or more effective than the parent compound," says Drake.

The trouble is there's no real way to tell this ahead of time—you have to do the work in the clinic to understand the mechanism and relate it to therapeutic and side effects. "The number of opportunities for new racemic switches are limited," says David Hipkiss, head of marketing at Ascot Fine Chemicals (Cambridge, UK). "And even if you go all of the way right to market…you have no guarantee that either yourself or your marketing partner will make that product a success."

Fundamentally, says Hipkiss, chirality is a key part of any biological process and consideration should be designed in from the start. "You would expect that in the main a product that is specifically designed to do a job would do better than a product that may be not designed so specifically." Indeed, final formulation sales for single-enantiomer pharmaceuticals increased 16% to $115 billion in 1999, accounting for a third of the $360 billion market, according to Technology Catalysts.

Nevertheless, analysts maintain that R-fluoxetine's case cannot be generalized. "The bottom line is that…it really says nothing about single isomers," says Richard Silver of Lehman Brothers. "The fact of the matter is drug development is risky no matter what…You have to look at every drug case by case."

Lilly's decision to pull out was certainly influenced by a US federal appeals court ruling in August that effectively means that Prozac loses patent protection in 2001, not 2003 as had been expected. Lilly had planned to switch its Prozac customers over to R-fluoxetine before 2003. With the R-fluoxetine side effects necessitating a re-trial at a lower dose—something that would take a couple of years—there was little point continuing because generics would hit the market before that trial was complete.

Meanwhile, Drake says with 14 other products in the clinic, Sepracor can easily compensate for its recent loss; "It's likely 6 to 9 new products will be approved in the next 4 years."

Emma Dorey

Dutch bill unlikely to revive industry

The Dutch parliament is currently considering a bill outlining the coalition government's position on biotechnology. Intended to boost investor confidence in the country's flagging biotechnology industry, the bill clarifies the country's position by bringing together in one document various efforts and policies already in operation. However, there is unlikely to be any real change in the industry until parliament is no longer dominated by factions that favor stringent biotech regulations. Nevertheless, all parties insist such a document is the best way forward.

The Dutch government has been a coalition of a social democratic party, the Partij van de Arbeid (PvdA), and two liberal factions—the right-wing Volkspartij voor Vrijheid en Democratie (VVD) and the Democraten '66 (D66) since 1998. Complaints from companies about conflicting strategies and inconsistent regulations from different government departments prompted Parliament to ask for this bill. "Five ministries and the EU are involved in biotechnology," says D66 member of parliament Pieter ter Veer, "Sometimes there is no coherence at all." The resulting document, *Integrale nota biotechnologie: kansen verantwoord en zorgvuldig benutten* is a joint effort by the minister of Economic Affairs (VVD), the minister of Agriculture, Nature and Fisheries (D66), the minister of Education, Culture and Science (VVD), the minister of Health (D66) and the only social democrat, the minister of Environmental Affairs (PvdA).

Reflecting Social Democrat views, the bill specifies no commercial release of crops containing antibiotic resistant genes, supports the labelling of GM food, and calls for a public debate in 2001 on biotechnology and food, and a broadening of the scientific advisory committee for GMO-releases to include social scientists, ecologists, and an ethics expert.

But from the economically minded Liberal side, the bill also outlines the effort already underway to create 75 new companies by 2005. 60 million guilders is being used to stimulate research on bio-informatics and genomics, and 100 million guilders (US$50 million) over four years on encouraging entrepreneurship by setting up incubators and educating young biotechnologists in commerce.

This move was prompted by concerns that the Netherlands lacks a 'booming' biotech region comparable to those around Wenen, Berlin, Gent, and Munich. Spending on biotechnology in Holland has dropped significantly from 380 million guilders (US$190 million) in the 1980s to only 11 million guilders between 1990 and 1994—the least amount spent by any European country with a significant biotech industry. Gerard van Beynum, chair of Economic Affairs advisory committee, attributes this in part to a loss of key government officials who understood the importance of a strong biotechnology industry.

Industry representatives hope that presenting a unified vision will also boost investor confidence. "More important than the money [for startups], is an improvement in the investment climate," says Ter Veer, "And that's the benefit of this Integral Document: with this the Dutch government has spoken out that biotechnology is important for the Netherlands."

However, the new bill will not change the fact that the Netherlands has one of the most stringent and confusing biotechnology policies in the EU. For instance, although protein therapeutics derived from genetically modified animals are socially acceptable, animal welfare concerns mean that cloning and genetic modification of animals (including mice) are allowed only if they are shown to be in the public's best interest and there isn't an alternative—something the Commission for Animal Biotechnology decides after a public hearing of each case. As a result, Pharming (Leiden), for example, chose the US over the Netherlands in 1997 to set up a subsidiary to develop transgenic cows. Yet the medical proteins from transgenic rabbits developed by Pharming (Belgium) are being tested against Pompe's disease in a Dutch hospital.

In addition, although the liberals and social democrats each comprise 30% of parliament, the social democrats are always supported by the Christian democratics (CDA) (20%), the Green and socialistic parties (10%), and the Christian parties (5%). Therefore, attempts to loosen restrictions governing biotech research are usually thwarted. This summer, for example, parliament voted against implementing the EU directive on patenting of GM animals and plants—an issue that is now being debated by the Council of State.

Nevertheless, PvdA member Willie Swildens is optimistic about the government's joint efforts. She still thinks it is possible to come up with a common vision of the part biotechnology has to play in the development of agriculture and health. "Sure, such an integral document is difficult to realize," she says, "But we hope this first document will play a role in the public debates"

Marianne Heselmans

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